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(52) UK CL (Edition P)
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C3M MXAT M162 M163 M200 M300
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(56) Documents Cited
GB 2255705 A **WO 96/10106 A1** **WO 95/17166 A1**
US 5460957 A **US 4582865 A**

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UK CL (Edition O) **C3M MXAT , C3U UCD UDA UDE**
INT CL^6 **A61K 31/725 47/36 , A61L 15/22 15/28 25/00 , C08B 15/00 37/00**
Online databases: WPI, CLAIMS

(54) Abstract Title
Gel for application to the human or animal body

(57) A gel and a process for the manufacture of a gel are disclosed, in which the gel consists of a first carboxy- polysaccharide (e.g. sodium pectate 601) and a second carboxy- polysaccharide (e.g. sodium carboxymethylcellulose 602) reacting with multivalent ions (e.g. calcium chloride 603) to produce a cross-linked hydrogel 604.

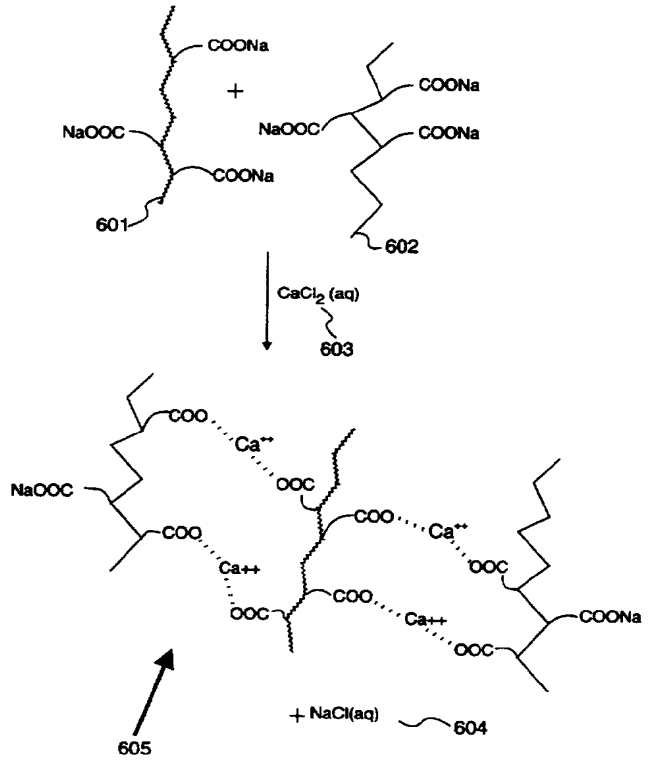

Figure 6

At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

This print takes account of replacement documents submitted after the date of filing to enable the application to comply with the formal requirements of the Patents Rules 1995

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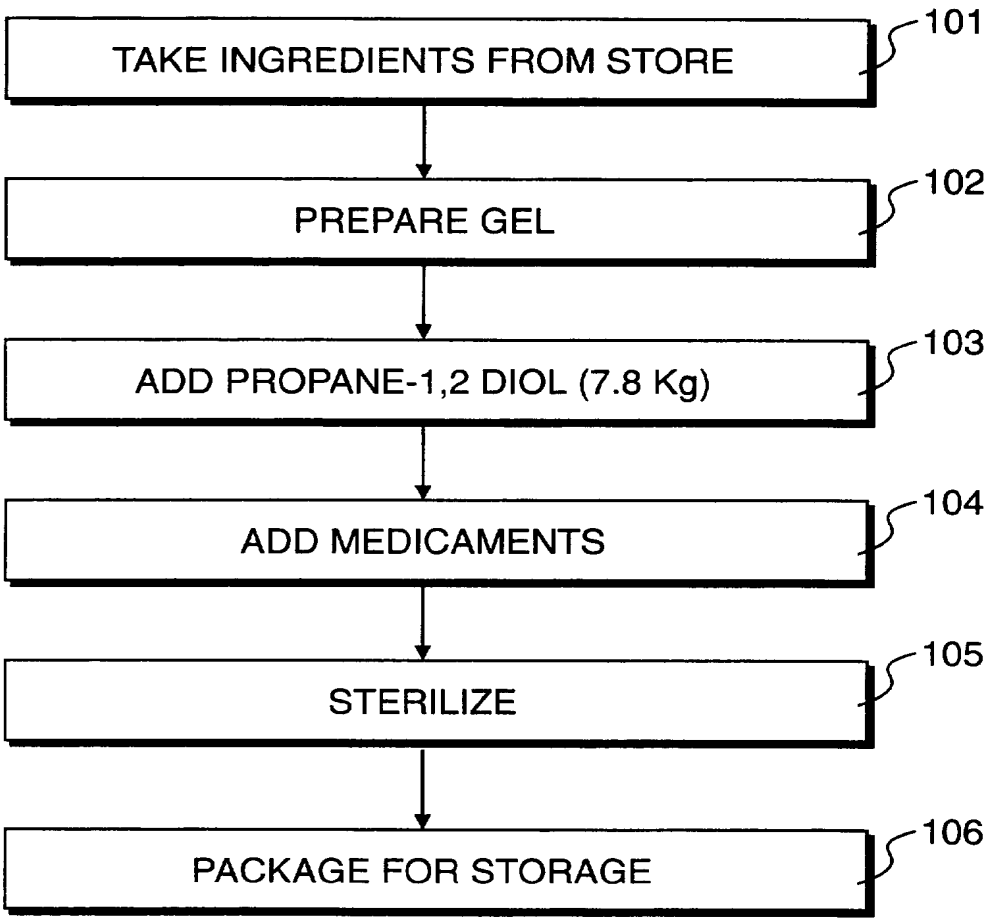

TAKE INGREDIENTS FROM STORE
101
PREPARE GEL
102
ADD PROPANE-1,2 DIOL (7.8 Kg)
103
ADD MEDICAMENTS
104
STERILIZE
105
PACKAGE FOR STORAGE
106

Figure 1

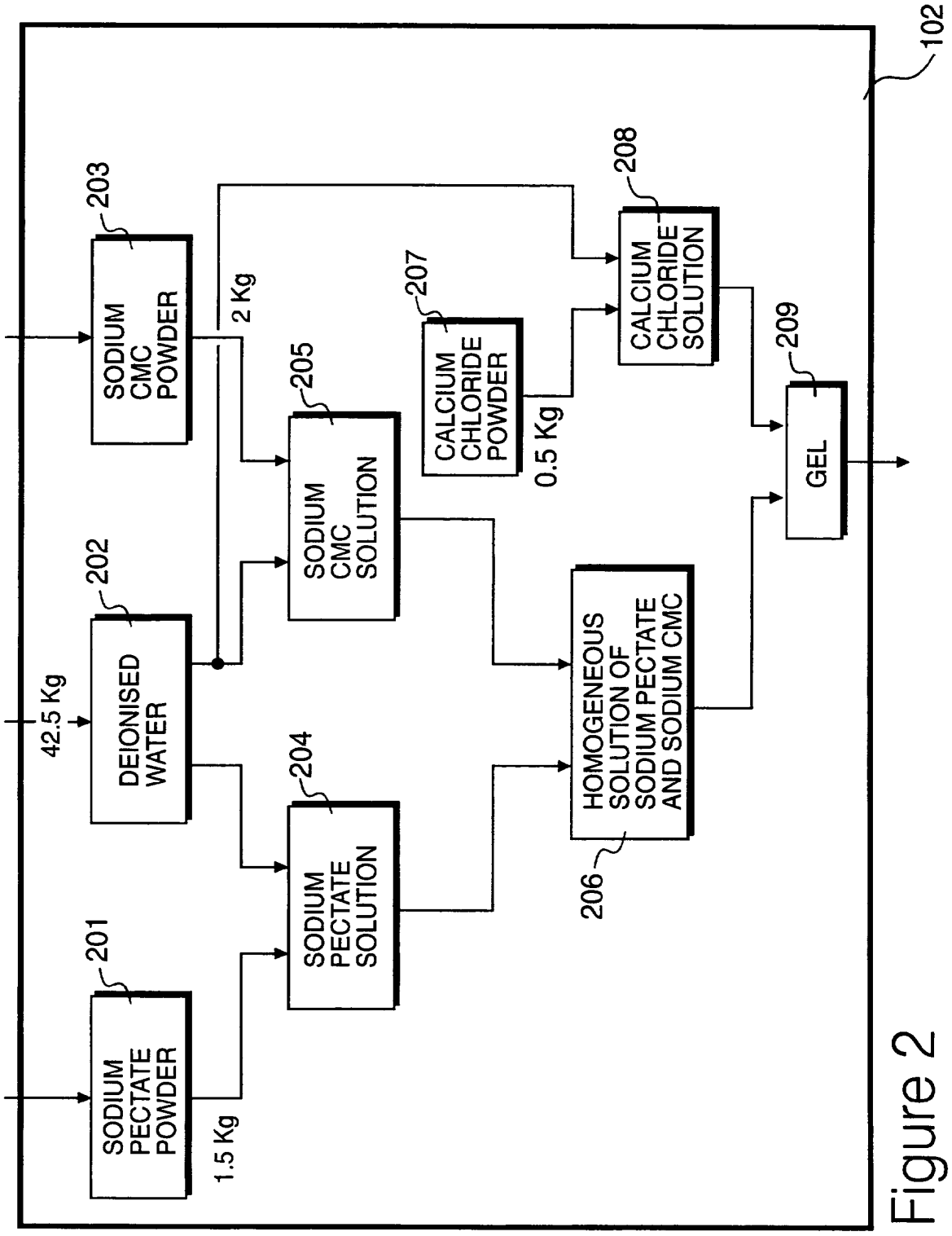

102
203
SODIUM CMC POWDER
2 Kg
208
CALCIUM CHLORIDE SOLUTION
207
CALCIUM CHLORIDE POWDER
0.5 Kg
205
SODIUM CMC SOLUTION
209
GEL
202
42.5 Kg
DEIONISED WATER
204
SODIUM PECTATE SOLUTION
HOMOGENEOUS SOLUTION OF SODIUM PECTATE AND SODIUM CMC
206
201
SODIUM PECTATE POWDER
1.5 Kg

Figure 2

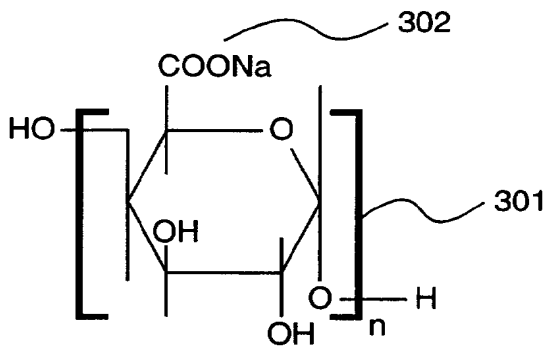


Figure 3

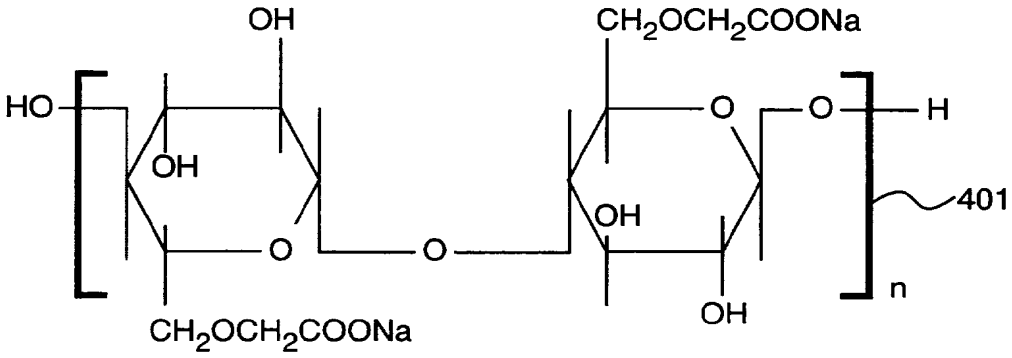


Figure 4

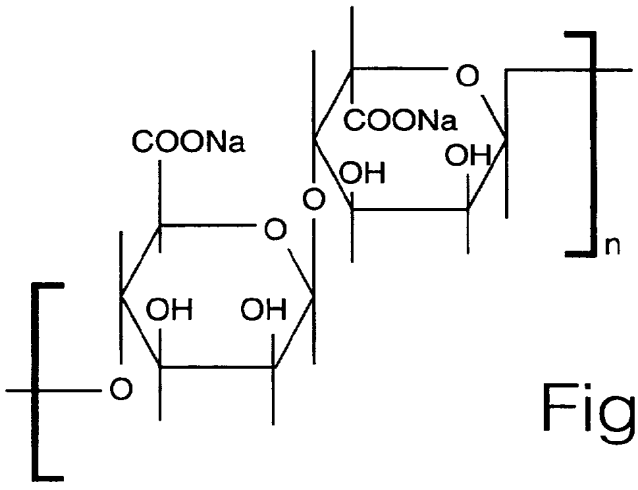


Figure 5

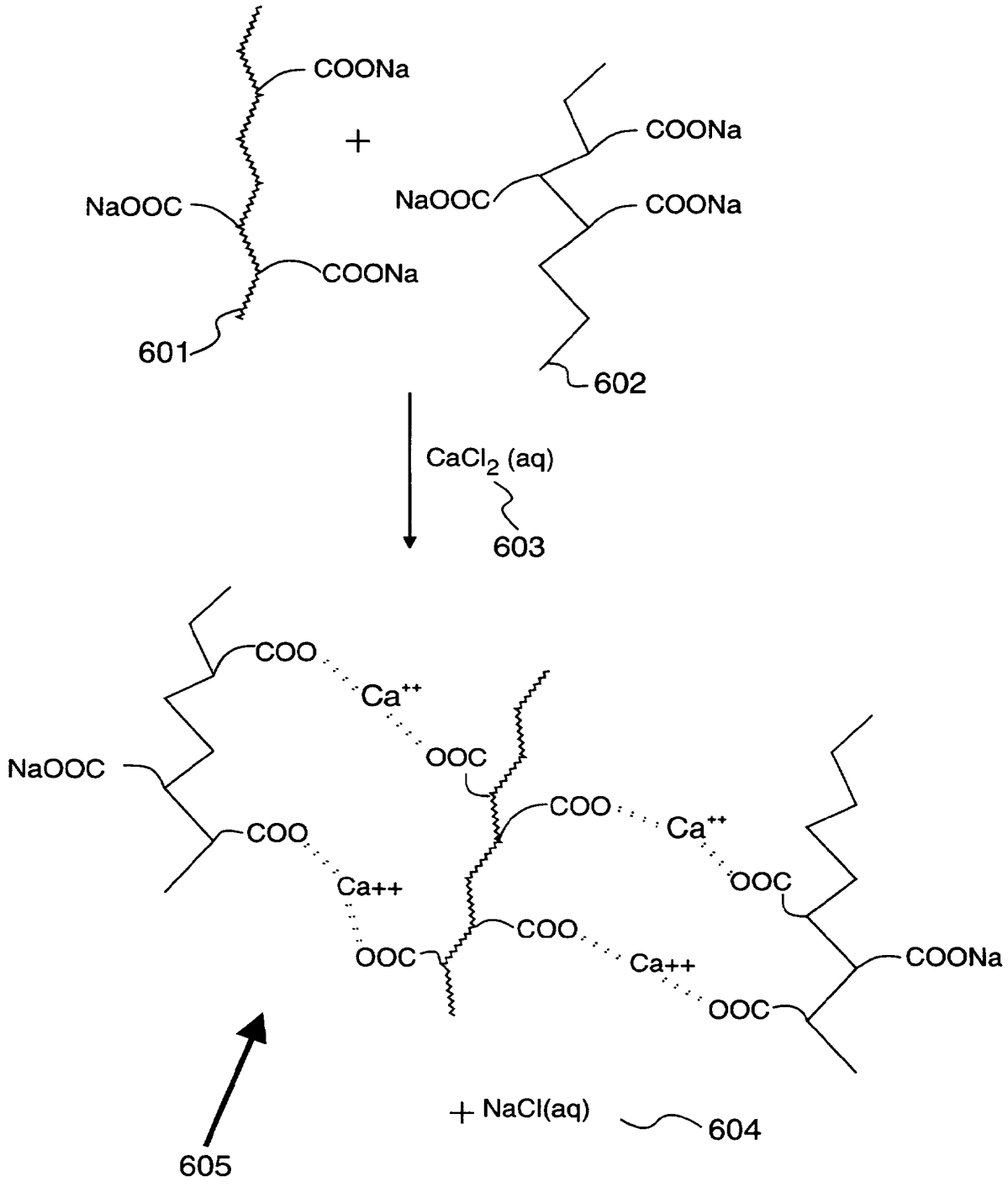
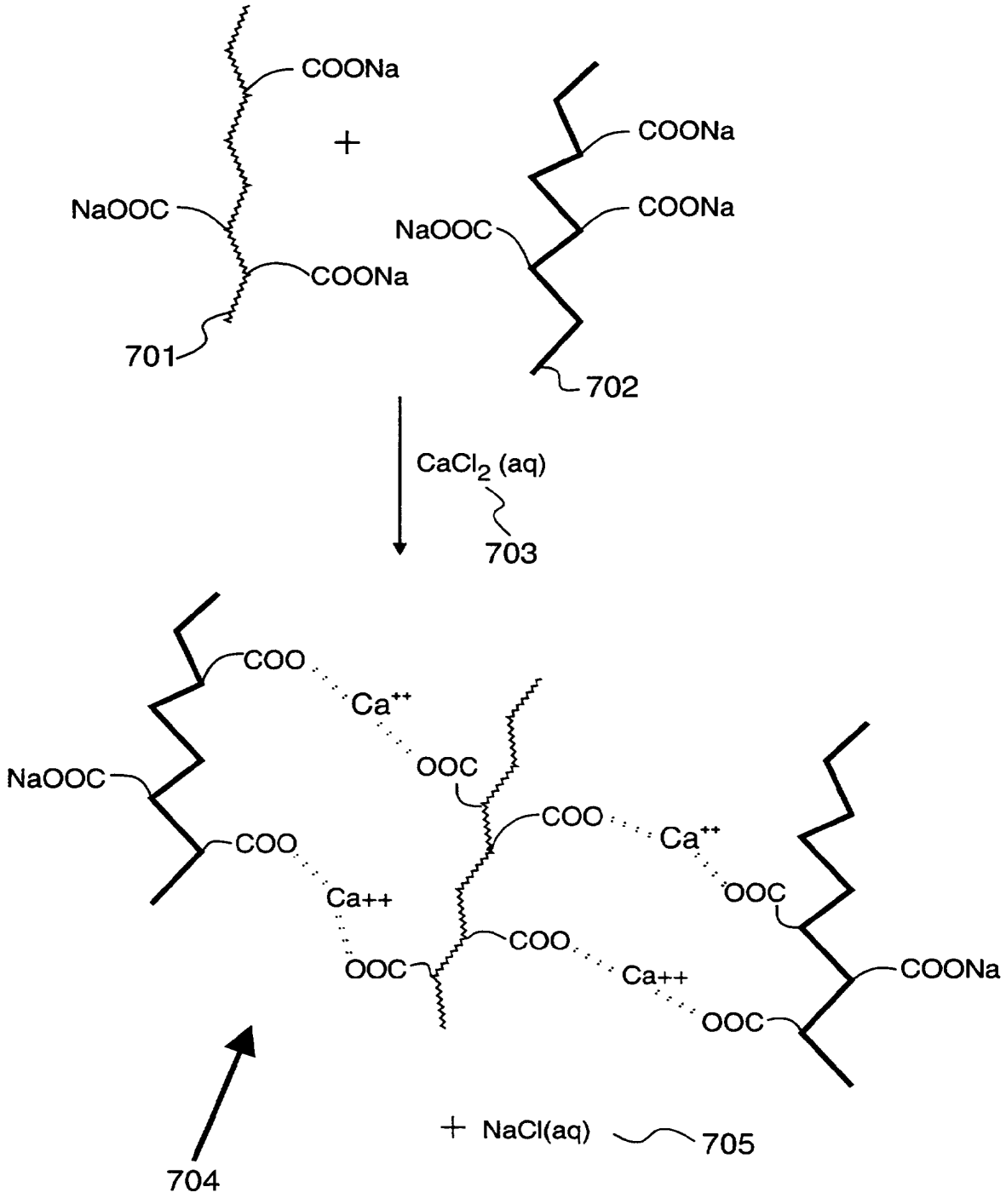

COONa
+
NaOOC
COONa
601
COONa
NaOOC
COONa
602
CaCl2 (aq)
603
COO
Ca++
NaOOC
OOC
COO
COO
Ca++
Ca++
OOC
COO
Ca++
OOC
COONa
OOC
+ NaCl(aq)
604
605

Figure 6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701
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COONa
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702
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NaOOC
OOC
COO
Ca++
COO
Ca++
OOC
Ca++
COO
Ca++
OOC
COONa
OOC
704
+ NaCl(aq)
705

Figure 7

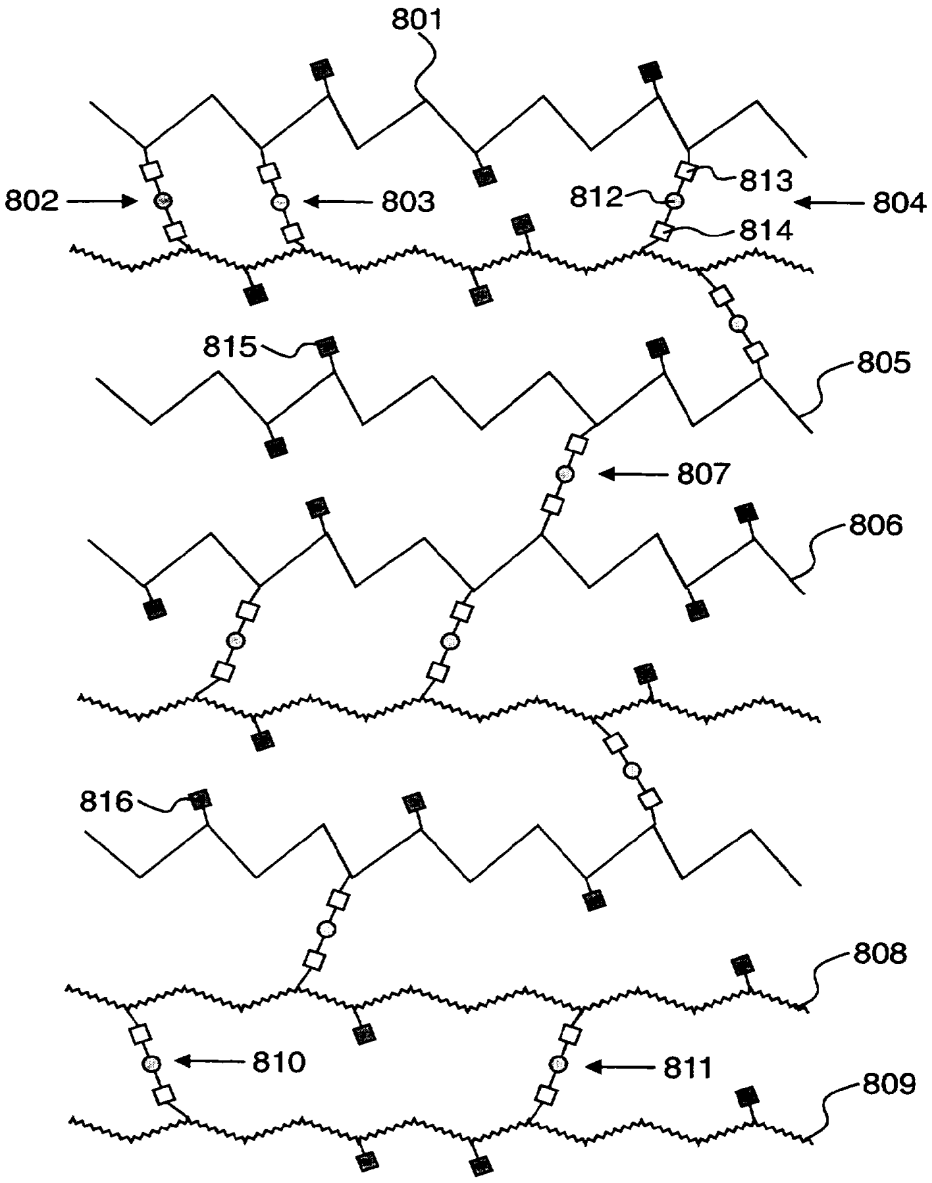

Figure 8

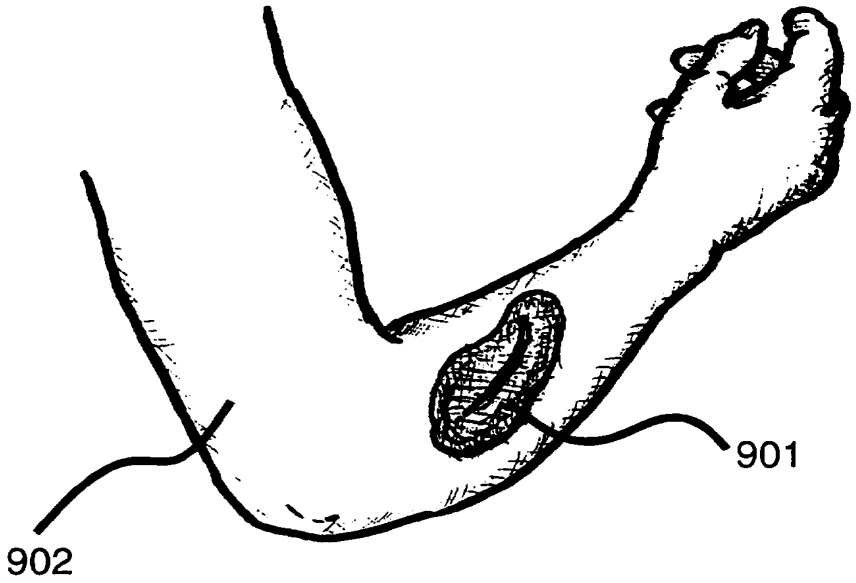

Figure 9

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GEL FOR APPLICATION TO THE HUMAN OR ANIMAL BODY

The present invention relates to a gel for application to the human or animal body, which may be suitable for application as a wound dressing.

Introduction

Hydrogels are known for the treatment of cuts, abrasions, burns and wounds etc, and consist of a matrix of polymers with a water content of up to 96%. Known hydrogel dressings exhibit less than ideal adherence characteristics and need to be covered with a secondary dressing, and the fluid or bacterial permeability of the gel depends upon the nature of the dressing used. Hydrogels are absorbent and semi-transparent and prior to application they may be refrigerated, such that the cooling effect contributes to the relief of pain.

A hydrogel for use as a wound dressing is described in International Patent Publication No. WO 92/16245, consisting of a water insoluble, water swellable cross-linked cellulose derivative, water and a polyol component. The gel described in this publication is primarily directed to the removal of necrotic tissue, as it reduces the need for the use of a chemical debriding agent or surgical excision. Thus, the known gel provides a dressing which can combine the actions of debriding and cleansing, independent upon the extent of necrosis. Furthermore, the dressing is capable of breaking down necrotic tissue and retaining resultant debris.

However, a problem with known hydrogels, for application as wound dressings, is that their adherency tends to be less than ideal. Furthermore, there is a tendency for these known compounds to disintegrate in the wound and to cause maceration of the skin around the wound.

Summary of The Invention

According to a first aspect of the present invention, there is provided a gel for application to the human or animal body, comprising a first carboxy-

polysaccharide, a second carboxy-polysaccharide and multivalent ions providing ionic cross-links between said carboxy-polysaccharides.

In a preferred embodiment the first carboxy-polysaccharide is a monovalent salt of a polygalacturonic acid derivative, wherein the preferred salt is sodium pectate.

Preferably, the second carboxy-polysaccharide is a monovalent salt of a carboxycellulose derivative such as sodium carboxymethylcellulose (sodium CMC). Alternatively the second carboxy-polysaccharide is a monovalent salt of an alginic acid derivative.

In a preferred embodiment, the multivalent ions are divalent. Preferably the divalent ions are ions of calcium or magnesium.

According to a second aspect of the present invention, there is provided a process for making a gel, comprising steps of preparing a solution including a first water soluble salt of a carboxy-polysaccharide and a second water soluble salt of a carboxy-polysaccharide; preparing a cross-linking agent in the form of a solution; and blending with said solution of carboxy-polysaccharides said cross-linking agent to form a gel through effecting formation of ionic bonds between said carboxy-polysaccharides. Preferably, the gel is blended with a polyol or diol component. In addition, further ingredients may be added, such as an anti-bacterial agent, an anti-fungal agent, an anti-mycotic agent, an anaesthetic, an additional debriding agent, an anti-inflammatory agent, a growth factor, an enzyme or nutrients.

Brief Description of The Drawings

Figure 1 shows an overview for the preparation of a hydrogel, including a gel preparation step;

Figure 2 details the gel preparation step identified in Figure 1, including the preparation of sodium pectate solution and the preparation of sodium carboxymethylcellulose solution;

Figure 3 details a sodium pectate polymer;

Figure 4 details a sodium carboxymethylcellulose polymer;

Figure 5 details a sodium alginic acid polymer;

Figure 6 illustrates the formation of cross-linkages between the polymers illustrated in Figures 3 and 4, when reacted with calcium chloride;

Figure 7 illustrates the formation of cross-linkages between the polymers illustrated in Figures 3 and 5, when reacted with calcium chloride;

Figure 8 illustrates, in two dimensions, a portion of gel composed of cross-linked polymers as detailed in Figure 6 or Figure 7.

Figure 9 illustrates the application of the gel produced by the process shown in Figure 1 applied to a wound.

Detailed Description of The Preferred Embodiments

The invention will now be described by way of example only with reference to the previously identified drawings.

An overview for the preparation of a hydrogel is shown in Figure 1. Initially, ingredients are required or taken from store at step 101, whereafter at step 102 a gel is prepared. At step 103 propane-1,2 diol is added to the gel to enhance its physical characteristics and to act as a preservative. Optionally, thereafter and as indicated at step 104, further medicaments may be added for particular applications. At step 105 the gel is sterilised by being maintained at a temperature of 121°C for a duration of at least twenty minutes. Thereafter, at step 106, the gel is packaged for subsequent application within a medical environment.

Step 102 for the preparation of the gel is detailed in Figure 2. Amounts described relate to a typical batch and may clearly be scaled during the manufacturing process to result in appropriate amounts being made. The amounts illustrated in Figure 2 require 7.8 kilograms (7.5 litres) of propane-1,2 diol being added at step 103, as illustrated in Figure 1.

The gel produced at step 102 essentially consists of a first carboxy-polysaccharide cross-linked with a second carboxy-polysaccharide, wherein the cross-linking is facilitated by the presence of multivalent ions. In the preferred embodiment, the preparation of which is illustrated in Figure 2, the

first carboxy-polysaccharide is sodium pectate and the second carboxy-polysaccharide is sodium carboxymethylcellulose. Sodium pectate suitable for the invention is for example supplied by Citrus Colloids Limited wherein no specific trade name is available, the compound interchangeably being called sodium pectate, sodium polypectate or sodium polygalacturonate. Similarly, suitable sodium carboxymethylcellulose powder is supplied by Hercules Limited under the Trade Name "Blanose Cellulose Gum", type 7H3SXF. 1.5 kilograms of sodium pectate powder 201 are dissolved in deionised water 202 to produce sodium pectate solution 204. A similar solution is made from 2 kilograms of sodium carboxymethylcellulose powder 203 to produce sodium carboxymethylcellulose solution 205. Deionised water is also added to 0.5 kilograms of calcium chloride powder 207 to produce calcium chloride solution 208, where the total weight of deionised water used for solutions 204, 205 and 208 amounts to 42.5 kilograms.

The sodium pectate solution 204 is mixed with the sodium carboxymethylcellulose solution 205 to produce a homogeneous solution shown at 206. The gel is then produced at 209 by adding, in a stepwise process with continual mixing, the calcium chloride solution 208, resulting in the establishment of cross-linkages produced by ionic bonding. Thus, in the preferred embodiment, the sodium ions of the carboxy-polysaccharides are attracted to the chloride ions of the calcium chloride to produce sodium chloride with the bivalent calcium ions attracting the carboxy groups of different and/or like polymers, thereby producing the ionic cross-linkages. The carboxy-polysaccharide salts are monovalent and may be sodium, potassium or ammonium for example. In the preferred embodiment as described above, sodium is the preferred salt.

In the above preferred embodiment the amount of cross-linking agent used is such that the gel exhibits characteristics suitable for adherence to a highly exudating wound. Reducing the amount of said agent produces gels of successively lower viscosity which are suitable for different applications and practices. For example in some countries less viscous gels are preferred for

treatment of deep highly exudating wounds and thus a gel according to the present invention which is suitable for these requirements can be made by reducing the amount of cross-linking agent used.

Incorporation of additional medicaments as described is facilitated in the invention through carboxy groups that are not incorporated into cross-linked ionic bonds. This is in addition to the simple trapping of said medicaments in the gel matrix. These medicaments may consist of an anti-bacterial agent, an anti-fungal agent, an anti-mycotic agent, an anaesthetic, an additional debriding agent or an anti-inflammatory agent. Alternatively, other agents may be added, such as a growth factor, an enzyme such as Lysozyme or a proteinase and nutrients such as vitamins, amino acids or trace elements. For example, it is known that the addition of zinc ions may be beneficial to assist in the healing process.

A sodium pectate polymer molecule is illustrated in Figure 3, in which the unit bounded by braces 301 is repeated to produce the polymer chain, typically consisting of more than 100 monomer units. Each monomer unit includes a sodium carboxy group 302 and it is the process of replacement of the sodium atoms of these groups which presents an ionised component for cross-linking with other polymer molecules.

A sodium carboxymethylcellulose polymer is shown in Figure 4, where again the repeating monomer is enclosed within braces 401. Each repeating monomer section includes cyclic components with each said component incorporating a sodium carboxymethyl group extending from each cyclic group. Again, some of the sodium atoms are removed thereby ionising the monomer units to facilitate the creation of cross-bonds with other polymers.

A sodium alginic acid polymer is shown in Figure 5, again having sodium carboxy groups from which a sodium atom may be removed to facilitate the creation of ionic cross-bonding.

The formation of cross-bonds or links between a sodium pectate polymer, of the type shown in Figure 3 and a sodium carboxymethylcellulose polymer, of the type shown in Figure 4, is illustrated in Figure 6. Sodium

pectate polymers 601 are placed in solution with sodium carboxymethylcellulose polymers 602. Aqueous calcium chloride 603 is added thereby placing calcium and chloride ions into the solution containing both sodium pectate and sodium carboxymethylcellulose polymers. The sodium ions present within the original polymers 601 and 602 are attracted to the chloride ions to produce aqueous sodium chloride 604, with the resulting free carboxy groups of the two polymers being attracted to the bivalent calcium ions. However, given that two carboxy groups are required in order to balance with each calcium ion, cross-linkages are formed between adjacent polymer strands, resulting in the production of the cross-linked hydrogel 605.

A similar reaction is shown in Figure 7 in which a sodium alginic acid polymer 702, functionally similar to polymer 602, reacts with a sodium pectate polymer 701. Again, aqueous calcium chloride 703 is added, resulting in the substitution of the monovalent sodium ions for bivalent calcium ions to produce an alternative cross-linked hydrogel 704 and sodium chloride 705.

A cross-linked hydrogel 605 is also shown in Figure 8. As shown in Figure 8, each polymer such as polymer 801 for example, may include a plurality of ionic cross-linkages and the total number of cross-linkages (802, 803 and 804 for polymer 801) within the gel will influence the viscosity of the gel, which, as previously stated, may be adjusted to satisfy particular medical applications and preferences.

The reactions shown in Figure 6 and Figure 7 consist of a first carboxy-polysaccharide forming a cross-linkage with a second carboxy-polysaccharide. However, as shown in Figure 8, cross-linkages are also formed between carboxy-polysaccharides of the same type. Two sodium carboxymethylcellulose polymers, 805 and 806 have a cross-link 807 and similarly two sodium pectate polymers 808 and 809 have two cross-links 810 and 811. As described above a cross-link such as cross-link 804 comprises a calcium ion 812 and two carboxy groups 813 and 814, one group being supplied from each polymer. Each carboxy-polysaccharide should have at

least one link to another carboxy-polysaccharide and it is not necessary for all of the potential bonding sites to be exploited. Two unused potential bonding sites (sodium carboxy groups) include 815 and 816 for example. This in turn facilitates the possibility of other groups being bound using a similar mechanism. However, not all of the bonding sites should be exploited for cross-linking otherwise there is a tendency for the gel to become hard and brittle.

The packaged gel identified at step 106 may be kept in storage for a period in the region of two years, provided that storage temperatures do not exceed 25°C.

The gel is particularly useful for application to relatively deep wounds, of the type illustrated at Figure 9. Wounds 901, in this example taking the form of a severe and deep dermal ulceration in a patient's arm 902 are often highly exudating or dry. The gel is therefore applied into the wound in order to prevent or at least reduce the amount of fluid oozing out of the wound site if highly exudating or to donate fluid if the wound is dry, and primarily to assist in the healing of the wound, aid removal of unwanted matter and to facilitate the prevention of undesirable contamination. Other wound categories applicable to this gel include, but are not restricted to, Stage I, II or III pressure ulcers, dermal ulcers, donor sites, second degree burns, abrasions, blisters and chronic wounds.

Prior to application of the dressing, the wound itself is irrigated with sterile saline solution, whereafter excess liquid is removed by an antiseptic swab. Gel, which may have been stored in a tube or sachet etc is squeezed into the wound to a minimum depth of 5mm, whereafter any excess gel is discarded. The tendency of the gel is to adhere to the wound, but it is necessary to apply a secondary dressing so as to maintain a moist, infection free environment. A further advantage of the invention is that the gel maintains structural integrity and thus does not readily disintegrate in environments such as highly exudating wounds. Removal of the dressing is simple and is facilitated by the fact that the dressing remains intact.

The tendency of the gel will be to remove excess liquid from its environment while ensuring that the environment does not dry out and thus remains moist. If the wound site is or becomes dry, the gel will tend to donate liquid to its environment ensuring that an equilibrium is maintained between the gel itself and its surrounding tissue.

The example given in the description of this embodiment concerning the proportions of the mixture may be varied to suit particular applications. In general, the carboxy-polysaccharide components, such as sodium pectate and sodium carboxymethylcellulose in the preferred embodiment, comprise at least 0.1% by weight of the total weight of the packaged gel.

The production process as described herein involves reactions and processes which take place at normal ambient temperatures. However, in some applications, it may be desirable to apply additional heating and/or other methods to the system in order to improve production times. An important advantage of the process described for making a gel according to the invention is that the carboxy-polysaccharides used as starting materials are water soluble. This facilitates mixing of components which in turn reduces costs in large scale processing.

The present invention is further illustrated by the following example of laboratory scale synthesis. A gel of the invention having the following composition was made:

Material	Weight	% by Weight
Sodium pectate	15g	2.78
Sodium carboxymethylcellulose (Blanose 7H3SXF)	20g	3.70
Calcium chloride	5g	0.93
Propylene glycol (Propane-1,2 diol)	78g	13.89
Deionised water	425g	78.70

15g of sodium pectate are stirred in 200ml of deionised water at room

temperature, until fully dissolved. Similarly, 20g of sodium carboxymethylcellulose are stirred in 200ml of deionised water, until fully dissolved. The two solutions are then mixed together until a homogeneous solution is formed. 5g of calcium chloride are dissolved in 25ml of deionised water, and added stepwise to the above solution. The mix is then homogenised carefully resulting in the formation of a highly viscous gel. Finally, 75ml of propylene glycol are added to the gel with continuous mixing, to ensure that a homogeneous gel is formed. The gel is then steam sterilised at 121°C for twenty minutes in an autoclave.

Claims

1. A gel for application to the human or animal body, comprising a first carboxy-polysaccharide a second carboxy-polysaccharide and multivalent ions providing ionic cross-links between said carboxy-polysaccharides.

2. A gel according to claim 1, wherein said first carboxy-polysaccharide is a monovalent salt of a polygalacturonic acid derivative.

3. A gel according to claim 1, wherein said second carboxy-polysaccharide is a monovalent salt of a carboxycellulose derivative.

4. A gel according to claim 1, wherein said second carboxy-polysaccharide is a monovalent salt of an alginic acid derivative.

5. A gel according to any of claims 2, 3 or 4, wherein said salts include ions of sodium, potassium or ammonium.

6. A gel according to claim 2, wherein said salt of said polygalacturonic acid derivative is sodium pectate.

7. A gel according to claim 3, wherein said carboxy-polysaccharide is sodium carboxymethylcellulose.

8. A gel according to claim 4, wherein said carboxy-polysaccharide is sodium alginic acid.

9. A gel according to any of claims 1 to 8, wherein said multivalent ions are divalent.

10. A gel according to claim 9, wherein said divalent ions are ions of calcium or magnesium.

11. A gel according to any preceding claim additionally comprising a polyol or diol component.

12. A gel according to claim 11 wherein said polyol or diol component includes propane-1,2 diol.

13. A gel according to any preceding claim used as a wound dressing or as a component of a wound dressing.

14. A gel according to claim 13 wherein said gel adheres to said wound, even if said wound is highly exudating.

15. A gel according to any preceding claim wherein the gel absorbs excess liquid from its environment whilst ensuring that the environment remains moist.

16. A gel according to any preceding claim wherein the gel donates liquid to its environment ensuring said environment remains moist.

17. A gel according to any preceding claim wherein said first and second carboxy-polysaccharides collectively comprise at least 0.1% by weight of the gel.

18. A gel according to any preceding claim wherein the gel is steam sterilised at a temperature greater than one hundred degrees centigrade.

19. A gel as claimed in any preceding claim wherein said gel

further comprises at least one of the following components: an anti-bacterial agent; an anti-fungal agent; an anti-mycotic agent; an anaesthetic; an additional debriding agent; an anti-inflammatory agent; a growth factor; an enzyme such as Lysozyme or a proteinase and/or simple nutrients such as vitamins, amino acids and trace metals such as a source of zinc ions.

20. A gel according to any preceding claim wherein carboxy-polysaccharide carboxy groups are not all incorporated in said cross-linked ionic bonds.

21. A gel according to claims 19 and 20 wherein said one or more additional components bind to said carboxy groups that are not incorporated in cross-links.

22. A process for making a gel, comprising steps of:

preparing a solution including a first water soluble salt of a carboxy-polysaccharide and a second water soluble salt of a carboxy-polysaccharide.

preparing a cross-linking agent in the form of a solution; and

blending with said solution of carboxy-polysaccharides said cross-linking agent to form a gel through effecting formation of ionic bonds between said carboxy-polysaccharides.

23. A process according to claim 22 wherein said solutions are prepared using deionised water.

24. A process according to claim 22 wherein said first carboxy-polysaccharide is a monovalent salt of a polygalacturonic acid derivative.

25. A process according to claim 22 wherein said second carboxy-polysaccharide is a monovalent salt of a carboxycellulose derivative.

26. A process according to claim 22 wherein said second carboxy-polysaccharide is a monovalent salt of an alginic acid derivative.

27. A process according to claims 24 to 26 wherein said salts are either sodium, potassium or ammonium.

28. A process according to claim 24 wherein said salt of polygalacturonic acid derivative is sodium pectate.

29. A process according to claim 25 wherein said salt of carboxy-polysaccharide is sodium carboxymethylcellulose.

30. A process according to claim 26 wherein said salt of an alginic acid derivative is sodium alginic acid.

31. A process according to claim 22 wherein said cross-linking agent is added in steps during blending with said combined solution.

32. A process according to claims 22 or 31 wherein said cross-linking agent is a divalent salt.

33. A process according to claim 32 wherein said divalent salt is a salt of calcium or magnesium.

34. A process according to claim 22 wherein said gel is blended with a polyol or diol component.

35. A process according to claims 22 or 34 wherein said gel has a collective carboxy-polysaccharide component comprising at least 0.1% by weight of the total weight of the components.

36. A process according to any of claims 22 to 35, wherein said gel is steam sterilised at a temperature greater than one hundred degrees centigrade.

37. A process for preparing a gel according to any of claims 22 to 36, wherein at least one of the following components is added: an anti-bacterial agent; an anti-fungal agent; an anti-mycotic agent; an anaesthetic; an additional debriding agent; an anti-inflammatory agent; a growth factor; an enzyme such as Lysozyme or a proteinase and/or simple nutrients such as vitamins, amino acids and trace metals such as for example a source of zinc ions.

38. A process according to any of claims 22 to 37, for making a gel to be used as, or as a component of, a wound dressing.

39. A gel substantially as herein described with reference to Figures 1 to 9.

40. A process for making a gel substantially as herein described.

The Patent Office

15

Application No:	GB 9704807.8	**Examiner:**	Alan Kerry
Claims searched:	1-40	**Date of search:**	12 June 1997

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): C3U UCD, UDA, UDE; C3M MXAT

Int Cl (Ed.6): C08B 15/00, 37/00; A61K 31/725, 47/36; A61L 15/22, 15/28, 25/00

Other: Online databases: WPI, CLAIMS

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	GB 2255705	(MARS GB) - see Claims 1-5	1
X	WO 95/17166 A1	(CALGON) - see Claim 1 and Examples	1, 3-5, 7, 8
A	WO 96/10106 A1	(INNOVATIVE TECHNOLOGIES) - see Claim 1 and Examples 1 & 2	
A	US 5460957	(HIURA et al) - see page 10, lines 12-67	1
A	US 4582865	(BALAZS et al) - see Claims 1-2 and Examples 1-13 & 18	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.